Best of the 2003 AUA Annual Meeting

Highlights from the 2003 Annual Meeting of the American Urological Association, April 26-May 1, 2003, Chicago, IL

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The Contributing and Medical Editors of *Reviews in Urology* were among the attendees at the 2003 American Urological Association (AUA) Annual Meeting in Chicago. Here, they present the latest developments in their respective areas of expertise.

Depression and Overactive Bladder

One of the most elegant presentations at this year's meeting of the AUA was a study convincingly establishing a link between overactive bladder (OAB) and depression.[1] William Steers, MD, of the University of Virginia, has been studying the role of serotonergic (5-HT) neurotransmission in the control of the lower urinary tract. It is well known that 5-HT neurotransmission is altered in some patients with depression. Dr Steers and associates studied the possibility of a link between altered bladder function and depression and whether this possible association could be evaluated in an animal model.

In a rat model of endogenous depression associated with OAB, the investigators tested the effect of the selective serotonin reuptake inhibitor fluoxetine on voiding frequency and awake cystometrogram (CMG) to determine if the overactivity could be reversed. Young rats were divided into 2 groups: clomipramine-treated pups and control pups. Each clomipramine-treated pup received injections of clomipramine hydrochloride (22.5 mg/kg SC bid) from postnatal day 8 to 21. Control pups received saline.

A standarized test for depression, the forced swim test, was used to detect the presence of depression. The voiding frequencies of both groups of pups were assessed at 15 weeks of age and awake CMGs were performed. Fluoxetine (10 mg/kg/d) was then administrated for 3 days to both groups, and voiding frequency and awake CMGs were repeated.

The investigators found that rats in the clomipramine-treated group voided more frequently than did those in the control group but that this difference was significant in female rats only. Awake CMGs of female rats in the clomipramine-treated group showed diminished bladder capacity and micturition volume compared with those of control rats. Fluoxetine treatment reversed increased voiding frequency in female clomipramine-treated rats, returning them to the levels seen in control rats. In the male control and clomipramine-treated groups, the effect of fluoxetine on voiding frequency was not significant. Awake CMGs in the female control group after fluoxetine treatment showed significantly increased bladder capacity and micturition volume (0.72 ± 0.10 mL to 1.29 ± 0.14 mL and 0.57 ± 0.10 mL to 1.03 ± 0.13 mL, respectively; $P < .05$).

Fluoxetine treatment reversed increased voiding frequency in female clomipramine-treated rats, returning them to the levels seen in control rats.

The key findings of Dr Steers and colleagues are that clomipramine treatment causes increased voiding frequency, decreased bladder capacity, and unstable bladder contractions in adult female rats. Fluoxetine reverses these effects. These results support the hypothesis that depression is linked to OAB and idiopathic urge incontinence.

[Kazumasa Torimoto, MD, Michael B. Chancellor, MD]

Nephrolithiasis

The genesis of calcium oxalate nephrolithiasis is thought to occur proximal to the renal collecting system. Some have hypothesized that calcium phosphate deposits within the kidney serve as a nucleating site for calcium oxalate. Andrew P. Evan, PhD, and colleagues reported results of 2 studies supporting this theory.[2,3]

The investigators obtained renal cortical and papillary biopsies at the time of percutaneous nephrolithotomy for 15 patients with idiopathic calcium oxalate nephrolithiasis and 4 patients with calcium oxalate stones associated with jejunal-ileal bypass. The tissue was analyzed with light microscopy, Fourier transform infrared, and x-ray diffraction techniques. Papillary tip calcifications, or plaque, were endoscopically mapped, and the percent plaque coverage of papillary tips was determined using digital imaging techniques. All subjects were also evaluated with 24-hour metabolic urine testing.

Although calcium salt deposition was identified in the renal papillae of subjects in both patient groups, the patterns of deposition were distinctly different. The calcium deposits in the idiopathic group originated in the basement membrane of the thin loops of Henle and spread though the interstitium, forming Randall's plaque–like deposits beneath the urothelium. In contrast, subjects in the small bowel bypass group had crystalline material in their medullary collecting ducts, extensive cellular damage, and interstitial inflammation. The crystalline material in both groups was apatite.[2] Plaque area was significantly greater in the idiopathic group. Urinary volume was negatively correlated with plaque area, whereas calcium excretion was positively correlated.[3]

These findings, which have recently been published in the *Journal of Clinical Investigation*,[4] suggest that a subepithelial apatite plaque may provide a scaffold for calcium oxalate nucleation in idiopathic calcium oxalate stone-formers. This process may play a less dominant role in other stone-forming populations. Further work is needed to characterize these processes at the molecular level.

[Dean G. Assimos, MD]

Recent Advances in the Treatment of CP/CPPS

Advances in our understanding of the enigmatic medical condition now known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS; category III prostatitis), including the development of standardized definitions and categorizations as well as a validated symptom index, have driven research in this clinical area over the last several years. This research is now paying off in terms of providing evidence-based data that we can use to develop management strategies for patients in clinical practice. At the 2003 meeting of the AUA, data from several well-designed, prospective trials evaluating some of the most common therapies for CP/CPPS were reported.

Antibiotic Therapy

Nickel and colleagues,[5] of the Canadian Prostatitis Research Group, conducted a multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of antibiotic therapy for CP/CPPS compared with placebo. Many uncontrolled trials have supported the use of antibiotics for treatment of this condition, and antibiotics remain the most common therapy prescribed for patients with prostatitis, despite the fact that cultures are usually negative. Men with a National Institutes of Health (NIH) diagnosis of CP/CPPS (specifically, no infection localized to the prostate) were randomized to receive levofloxacin, 500 mg/d, or placebo for 6 weeks; patients were followed for 6 weeks after therapy was discontinued. Although the patients who received antibiotic thera-

py experienced a progressive improvement in symptoms, so did those who received placebo and, at 6 weeks, there was no statistically or clinically significant difference between the 2 groups in improvement in NIH Chronic Prostatitis Symptom Index (CPSI). Similarly, the responder rate in the levofloxacin group was not statistically significantly different from that in the placebo group. Study subjects, on average, had symptoms of CP/CPPS for over 5 years, and more than 80% of subjects had previously received antibiotic therapy. In this particular group of patients, it appears that antibiotic therapy is no better than placebo. However, patients recently diagnosed with CP/CPPS and naïve to antibiotic therapy may respond to an initial empiric course of antibiotic therapy.

α-Blocker Therapy

Two prospective, randomized, placebo-controlled trials evaluated α-blocker therapy for CP/CPPS.[6,7] α-Blockers are among the most common treatments of CP/CPPS, yet few data are available regarding their efficacy in this clinical setting compared with placebo. Mehik and colleagues[6] randomized patients to alfuzosin, 5 mg bid, or placebo and compared these groups with a standard-therapy group (supportive therapy, antiinflammatory therapy, heat therapy, etc) during an active 6-month treatment phase and a 6-month follow-up phase. At the end of 6 months of active therapy, the alfuzosin group had a significant decrease in total CPSI score compared with both the placebo group and the control/standard-treatment group (9.9, 3.8, and 4.3 decrease in CPSI score, respectively; $P = .01$). A statistically and clinically significant difference between the groups was not seen until patients had received 4 months of treatment. At 6 months, alfuzosin and placebo were discontinued, and symptom scores in all domains of the CPSI showed deterioration in these groups. The investigators concluded that 6 months of alfuzosin therapy for CP/CPPS is safe and well-tolerated and results in modest but significant improvement in symptoms (particularly in the pain domain) compared with placebo and standard/traditional treatment. The beneficial effect was apparent only after several months of therapy and disappeared when treatment was discontinued.

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Chea and associates[7] evaluated the long-term effectiveness of terazosin therapy for CP/CPPS. Patients with CP/CPPS were randomized to terazosin or placebo in a 14-week double-blind study. The primary response criterion was an improvement in the NIH CPSI quality-of-life domain. Based on this criterion, after 14 weeks of initial therapy, 56% of subjects who received terazosin responded, compared with 33% of those who received placebo ($P = .03$). Of the 23 responder subjects in the terazosin group, 22% relapsed over the following 6 months, whereas 50% of the placebo responders relapsed. This study, with its long-term follow-up, confirmed the finding of Mehik and colleagues[6] that long-term therapy with α-blockers is required to achieve a treatment effect and to prevent relapse.

Herbal Therapy

Many patients with CP/CPPS initiate phytotherapy (herbal remedies), and most do so in the absence of medical supervision. Reissigl and associates[8] evaluated the efficacy and safety of *Seranoa repens* (saw palmetto) in patients with CP/CPPS. Men with category IIIB (non-inflammatory) CP/CPPS were randomized to 6 weeks of active treatment with saw palmetto or to a control group. Response to therapy was evaluated at 6 weeks and 12 weeks after treatment. Seventy-five percent of patients in the saw palmetto group had at least mild improvement, compared with 20% of those in the control group. Fifty-five percent of patients in the saw palmetto group reported moderate or marked improvement, compared with 16% of those in the control group. Patients who received saw palmetto had a 30% reduction in total CPSI; however, 12 weeks after therapy was discontinued, there was no difference in symptom score between the groups. Results of this study suggest that saw palmetto may provide some clinical benefit in patients with category IIIB CP/CPPS, but treatment must be prolonged.

Immune Modulation

Dimitrakov and Dikov[9] examined the possibility that mycophenolate mofetil, an immunosuppressant used in kidney transplantation patients, may alleviate symptoms of CP/CPPS. Men with category IIIB CP/CPPS were randomized to receive mycophenolate mofetil or placebo. After 1 month of treatment, there was a significant decrease in pain scores for the treatment group compared with the placebo group ($P < .001$). Eighty-five percent of patients in the mycophenolate group reported improvement at the end of 1 month, compared with 25% of those in the placebo group ($P < .001$). This effect appeared to be sustained at 6 months, when 65% of subjects in the active treatment group continued to report sustained improvement, compared with 15% of

subjects in the placebo group. The investigators concluded that immunosuppressive medications, such as mycophenolate mofetil, may have an important role in the future treatment of CP/CPPS; however, further studies are needed.

Heat Therapy

Small pilot studies of transurethral microwave thermotherapy (TUMT) for CP/CPPS have had variable results. Kastner and colleauges[10] randomized 40 patients with chronic abacterial prostatitis to TUMT (Targis™ System, Urologix, Inc, Minneapolis, MN) with a peak intraprostatic temperature of either 55ºC or 70ºC. Although the trial is ongoing, 35 patients have completed the 6-month follow-up. More than 50% of these patients had improvement (defined as 50% improvement in CPSI) in terms of pain, urinary symptoms, and quality of life. Side effects were minor and transient, and the lower treatment temperature appeared to be comfortable. The investigators concluded that longer follow-up in a larger future trial is required to evaluate treatment durability and placebo effect.

Summary

The prostatitis section of the 2003 AUA was an exciting venue this year. Science, in terms of well-designed prospective trials, has finally entered the prostatitis field. Data from future and ongoing trials, including the soon-to-be-reported NIH Chronic Prostatitis Collaborative Research Network's study evaluating antibiotics and α-blockers, will be reported in the next year or so. The studies presented at this year's AUA evaluating antibiotics, α-blockers, herbal therapies, immune modulation, and heat therapy finally provide data that can be applied to clinical practice.

[J. Curtis Nickel, MD, FRCSC]

Urologic Oncology

The 2003 annual meeting of the AUA featured multiple oral and poster sessions dedicated to basic and clinical research abstracts, submitted from researchers throughout the world, relating to bladder, kidney, penile, testis, and urethral cancers. The meeting was broadly organized into sessions devoted to basic research, evaluation and treatment, detection and screening, as well as podium sessions and abstracts on surgical aspects of urologic oncology.

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Renal Cell Carcinoma and TNM Staging

The American Joint Commission on Cancer TNM (tumor-node-metastasis) pathologic staging system continues to evolve to accommodate changing data relating to the optimal grouping of variables into categories having similar prognostic significance.[11] Several abstracts pointed out deficiencies in the current classification scheme and suggested alternative groupings. Data from 2 abstracts indicated that the current T3a classification, which includes patients with renal fat invasion as well as patients with direct invasion into the adrenal gland, may need to be revised.

Patel and colleagues,[12] from Memorial Sloan-Kettering Cancer Center, presented data on 1271 patients with renal cell carcinoma (RCC). Kaplan-Meier analysis of disease-specific survival revealed that, for patients with adrenal involvement, median survival was only 26 months; this was similar to the median survival of patients with a T4 classification and significantly worse than that of patients with tumor involvement of only the perinephric fat (>120 months).

These findings were mirrored by data presented by Han and colleagues,[13] from the University of California, Los Angeles, who placed third in the Clinical Research Essay Contest. In an analysis of 1087 patients who underwent nephrectomy, the investigators found cancer-specific survival rates of patients with T3a-perirenal fat tumors to be significantly better than those of patients with direct adrenal involvement, which was again indistinguishable from the survival curve of T4 patients who had direct invasion of other adjacent organs.

Data from Germany, presented by Dreihaupt and colleuges,[14] provide evidence that the current size criteria (7 cm) separating T1 and T2 tumors is too large. Based on an analysis of 437 patients with T1 and T2 tumors who were operated on between 1992 and 2001, the authors suggest that the tumor diameter cutoff size be lowered to 4 cm, a conclusion that reflects current thinking that a better cutoff point lies somewhere between 4 cm and 5 cm.

Moinzadeh and Libertino[15] presented data from the Lahey Clinic showing that the survival of patients with RCC invading the renal vein was better than that of patients with invasion of the inferior vena cava (IVC), but that the level of IVC involvement was not a significant stratification factor. Their findings suggest that patients with IVC involvement below the diaphragm be moved from the current T3b classification into the current T3c classification.

Molecular Markers

This year was a banner year for abstracts investigating chromosomal, molecular, proteomic, and gene expression patterns of tumors—a reflection of the increasingly sophisticated methods of tumor analysis. A number of groups presented data using DNA microarray analysis to address significant clinical questions relating to bladder cancer. Of interest, both an Oxford study,[16] which used the Affymetrix UI33A GeneChip®, and a Mayo Clinic study,[17] which used the Affymetrix U95A GeneChip®, identified osteopontin as a gene involved in the invasive bladder cancer phenotype; results were further verified through the use of reverse transcriptase polymerase chain reaction (RT-PCR) and enzyme linked immunoassay of whole tumor protein extracts. The Oxford group presented results of gene cluster analysis suggesting that high-grade T1 tumors have gene expression profiles similar to muscle invasive tumors.

Saint and colleagues[18] presented results of a multi-institutional study using the Affymetrix U133A microarray to predict response to bacille Calmette-Guérin (BCG) therapy in patients with bladder cancer. Thirty-seven genes were ultimately found able to distinguish responders from nonresponders; the identified genes included genes associated with interferon-induced proteins and intracellular signaling pathways, such as the TGF-beta pathway.

In a podium presentation that won second prize for clinical research, Matthew Bui, MD, PhD, of the University of California, Los Angeles, presented the results of a tissue-array study examining the significance of carbonic anhydrase IX (CA IX) in RCC.[19] CA IX monoclonal antibody staining was assessed on tissue microarrays of specimens from 321 RCC patients undergoing nephrectomy. Decreased CA IX levels were found to be an independent predictor of poor survival in patients with advanced RCC. In addition, CA IX status was found to be useful in identifying patients with localized RCC at high risk for developing metastatic disease and as a possible molecular marker for predicting response to immunotherapy.

A number of groups presented abstracts examining other aspects of CA IX and kidney cancer, reaffirming its position as the most important RCC-associated antigen discovered to date. Both Sharma and colleagues,[20] from Chandigarh, India, and Gilbert and colleagues[21] presented data on CA IX gene expression in the peripheral blood. Blood samples from RCC patients were analyzed for CA IX gene expression by RT-PCR to detect the presence of circulating cancer cells. Data from both studies suggest that postoperative persistence of peripheral blood CA IX gene expression is of value in predicting the likelihood of clinical disease recurrence.

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Bleumar and associates[22] reported the latest data from a phase I/II clinical study of a chimeric monoclonal antibody that targets the CA IX cell surface antigen in combination with daily low-dose interleukin-2 in 36 patients with metastatic RCC. After 12 weeks of treatment, no patient experienced grade 3 or 4 toxicity or developed human anti-chimeric antibodies; 8 patients experienced disease stabilization; and 3 patients experienced partial remission.

Clinical Trials and New Treatment Strategies

Data from several noteworthy phase III clinical studies were presented at this year's meeting. Lerner and colleagues[23] presented results of a retrospective analysis of data from a study conducted by the Southwest Oncology Group in which 593 subjects were randomized to receive BCG with or without maintenance therapy. Patients who achieved a complete response during BCG induction had a 77% 5-year survival probability, compared with 61% for those who did not have a complete response; failure to achieve a complete response represented a significant risk of disease progression and death for patients with carcinoma in situ or recurrent Ta or T1 bladder cancer.

Sylvester and associates[24] presented important quality-of-life treatment-toxicity data from a phase III trial of maintenance BCG therapy conducted by the European Organization for Research and Treatment of Cancer Genito-Urinary Group. The study, which included 520 patients, failed to confirm previous reports suggesting that patients with BCG-related toxicity enjoy a better clinical outcome than those without such toxicity.

O'Donnell and colleagues[25] presented interim results of a national, multicenter phase II trial of combination BCG plus interferon alfa-2B for the treatment of superficial bladder cancer. Results support previous reports suggesting an enhanced efficacy of combination BCG plus interferon as upfront and salvage therapy for patients with moderate- to high-risk superficial bladder cancer and those who have failed BCG therapy.

Two basic research abstracts presented alternative strategies for improving the outcomes of gene ther-

apy for bladder cancer. Intravesical gene therapy using adenoviral vectors has proved to be limited by the relative lack of expression of the coxsackie and adenovirus receptor (CAR) on bladder epithelium, which is necessary for virus binding and gene transcript delivery. Matsumoto and colleauges,[26] from Baylor University, described a chimeric adenovirus vector utilizing the Ad35 fiber gene that conferred a CAR-independent cell-entry mechanism to the adenovirus. Transfection of the herpes simplex virus thymidine kinase gene and treatment with the suicide gene therapy prodrug ganciclovir enhanced killing 30-fold compared with wild-type adenovirus in CAR-negative cell lines.

Sachs and colleagues[27] presented an alternative strategy using valproic acid, a histone deacetylase inhibitor capable of overcoming CAR gene inactivation. Using this approach, the CAR copy number was increased 13-fold, resulting in 66% of cells expressing CAR on their cell surface, compared with only 3% of untreated cells, and leading to a 38-fold increase in transgene expression.

Rapamycin, an immunosuppressive drug used in patients undergoing kidney transplantation, and its analogues have shown promise in early-phase clinical trials of patients with metastatic RCC. Sadukhan and colleagues,[28] from Cleveland, Ohio, presented important preclinical data that may provide insight into the mechanisms underlying this treatment strategy. MSKRCC54 cells, a human RCC cell line, were treated with escalating doses of rapamycin, and cell confluence, cell viability, and apoptotic assays were performed. Results demonstrated a 50% inhibition of cell growth with 48 hours of rapamycin, 50 ng/mL, and total inhibition of growth with 48 hours of rapamycin, 100 ng/mL. It was suggested that both antiproliferative and apoptosis-inductive mechanisms contributed to this effect. Because rapamycin is currently used as an immunosuppressive agent following renal transplantation, it is provocative to speculate whether it may exert a chemopreventive effect to decrease the risk of transplantation-associated RCC.

Several abstracts presented new strategies of immunotherapy for RCC. Schwaab and associates[29] presented results of a phase II trial of monthly, subcutaneous injections of autologous tumor vaccine combined with daily injections of granulocyte-macrophage colony-stimulating factor in patients with advanced RCC. Twenty-two patients with stage III or stage IV RCC received this treatment regimen. Treatment was well-tolerated, and there was evidence of statistically significant modulation of CD4 and CD8 tumor-specific T-cell precursors. Among the patients with metastatic disease, 1 patient achieved complete regression, 5 had stable disease, and 7 had progressive disease. Nine patients without metastatic disease who were treated in an adjuvant setting have remained disease-free. Confirmation of these results will require larger, randomized studies.

[Allan J. Pantuck, MD, Arie S. Belldegrun, MD, FACS]

Prostate Tumor Markers

Once again, prostate tumor markers comprised a dominant theme at the 2003 meeting of the AUA. In all, 152 papers on this topic were presented (8.1% of all papers presented). Major themes included lowering the prostate-specific antigen (PSA) cutoff for biopsy, the utility of complexed PSA (cPSA), repeat biopsy, monitoring of patients with prostate cancer, and novel markers.

It is well recognized that the use of a total PSA (tPSA) level of 4.0 ng/mL as a cutoff point for biopsy recommendation was not scientifically determined. Moreover, it has been established that a large number of men with significant prostate carcinomas have PSA levels below 4.0 ng/mL. Indeed, the incidence of prostate carcinoma in most large biopsy series of men with PSA levels between 3.0 ng/mL and 4.0 ng/mL is indistinguishable from that in men with levels between 4.0 ng/mL and 5.0 ng/mL. However, when the PSA threshold is lowered, lack of specificity (false-positive PSA results) becomes increasingly problematic.

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Complexed PSA

A study by Brawer and associates[30] demonstrated that the use of cPSA measurement significantly improved specificity over the use of tPSA measurement. In a multicenter trial, the investigators evaluated the performance of cPSA measurement in 316 men with tPSA levels of 2.6 ng/mL to 4.0 ng/mL who were scheduled for prostate biopsy. Eighty-two subjects (25.9%) were diagnosed with prostate cancer using a cPSA cutoff of 2.3 ng/mL or a tPSA cutoff of 2.73 ng/mL. Using these cutoff values to provide 95% sensitivity, cPSA level provided twice the specificity as tPSA level (20.1% vs 9.8%, respectively). In a subset of 205 men who also had a free PSA (fPSA) measurement, there was no benefit of the free/total PSA ratio (f/t PSA) compared with cPSA alone in differentiating subjects with or without cancer.

Kobayshi and colleagues[31] investigated the clinical usefulness of cPSA measurement in men with tPSA levels between 2.5 ng/mL and 4.0 ng/mL. They demonstrated that the use of cPSA level was no different than tPSA level or f/t PSA in their overall biopsy series of 197 patients; in men who had a tPSA level between 2.1 ng/mL and 3.7 ng/mL, test specificity was enhanced with the use of cPSA.

Zhang and associates[32] used artificial intelligence with a nonlinear model combining cPSA, total prostate gland volume, and age, for the prediction of prostate cancer in men with tPSA levels between 2.0 ng/mL and 4.0 ng/mL. The study utilized the Bayer-sponsored 7-site prospective evaluation of the complexed form of PSA. Of 205 men evaluated, 51 (25%) had prostate cancer. Patients were distributed into a randomly selected training set (n = 119) and an independent test set (n = 86). At a sensitivity of 82.4%, the model utilizing cPSA, total gland volume, and age demonstrated a specificity of 49.3%. In contrast, at the same sensitivity, a model utilizing tPSA, percent fPSA (%fPSA), total gland volume, and age demonstrated an inferior specificity of 34.8%. This study confirms the enhanced performance of cPSA measurement in this low PSA range and the importance of nonlinear models. Of course, evaluation of this model in an independent cohort is needed before definitive statements can be made.

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PSA Threshold

Haese and associates[33] evaluated 1602 men to determine whether lowering the PSA threshold would necessitate a greater number of biopsies to detect cancer. Men with PSA levels of 2.0 ng/mL to 4.0 ng/mL were compared with men with PSA levels between 4.0 ng/mL and 10.0 ng/mL. Results demonstrated that, for men in the 4.0 ng/mL to 10.0 ng/mL range, 3 biopsies were needed to detect 1 cancer; for those in the 2.0 ng/mL to 4.0 ng/mL range, 5 biopsies were needed to detect 1 cancer. However, when using a %fPSA cutoff of 18% to 20% in the latter group of men, half of men biopsied would have malignancy.

Capitalizing on the St. Louis large serial screening cohort, Zhu and colleagues[34] examined the utility of biopsy in men with tPSA levels of 2.6 ng/mL to 4.0 ng/mL. A total of 20,788 men with an initial PSA value less than 2.6 ng/mL were enrolled in the screening study; 523 (2.5%) of these men had PSA levels that subsequently rose above this threshold, underwent biopsy, and had prostate cancer detected. Of the 523 men, 297 had radical prostatectomy and, among these men, 223 had cancer detected while their tPSA level was 2.6 ng/mL to 4.0 ng/mL and 74 had cancer detected after the level rose above 4.0 ng/mL. The men who had cancer detected while in the lower tPSA range had more favorable pathology; however, this did not achieve a statistically significant level. Furthermore, the incidence of PSA progression was indistinguishable between these 2 cohorts.

This study calls into question whether detecting cancer in this lower PSA range is indeed necessary. Rather, it may be possible to delay detection until a higher PSA level is reached and still achieve a cure. Further follow-up is necessary to determine whether the long-term progression-free interval and, most important, prostate cancer–specific mortality differ between these 2 groups of patients.

Preoperative PSA and Biochemical Progression

Roehl and associates[35] examined whether preoperative PSA level correlates with the interval to biochemical progression following radical prostatectomy. A total of 840 men who underwent radical prostatectomy were subsequently evaluated and found to have biochemical progression, defined as a PSA value of greater than 0.2 ng/mL. The median time to progression for men who had a preoperative PSA level less than 2.6 ng/mL was 37.5 months. Among men with a preoperative PSA level between 4.0 ng/mL and 10.0 ng/mL, median time to progression was 30 months. If the preoperative PSA level was higher than 20 ng/mL, median progression time was 15.5 months. The authors concluded that preoperative PSA level is a significant predictor of biochemical progression after radical prostatectomy. However, it must be emphasized that the study does not clearly demonstrate the prognostic impact of PSA level, as men who did not progress were not included.

In another study, Stamey and associates[36] evaluated 159 men with PSA levels less than 4.0 ng/mL who underwent radical prostatectomy. One hundred thirty-two men were found to have pure peripheral zone cancer and, of these men, 125 had adequate PSA follow-up. Results showed no difference in preoperative PSA level between men who were cured and those who had biochemical failure. Preoperative serum PSA level reflected neither cancer volume nor the amount of Gleason grade 4 or 5 cancer.

Repeat Biopsy

Another major theme of the session

on prostate tumor markers was repeat prostate needle biopsy. Indeed, men being evaluated after initial negative biopsy present a significant clinical problem for practicing urologists. Bartsch and associates[37] evaluated 264 men who underwent repeat ultrasound-guided prostate needle biopsy consisting of at least 10 cores of tissue. The authors evaluated tPSA, cPSA, and f/t PSA as predictors of prostate cancer. Ninety-one men (34%) had cancer detected on the repeat biopsy. Using area-under-the-curve analysis, cPSA level was a significantly greater predictor of cancer than was tPSA level (P = .017), and the complexed/total PSA ratio was a greater predictor than was cPSA level (P = .03). There was no difference between the use of f/t PSA or cPSA alone. This study confirms the previous observation that cPSA is a useful predictor in assessing the likelihood of a missed carcinoma after initial prostate needle biopsy.

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Rhoden and Morgentaler[38] reported data from an important study of prostate biopsy in men with low serum testosterone levels. A total of 264 men with serum testosterone levels less than 300 ng/dL and tPSA levels less than 4.0 ng/mL underwent prostate biopsy. Malignancy was detected in 39 cases (14.8%). There were no differences between men with and without cancer with respect to age, serum testosterone level, or free testosterone level. PSA levels and the prevalence of prostatic intraepithelial neoplasia were higher in men with cancer. This study demonstrates a high rate of cancer detection in men with low serum testosterone levels and PSA levels less than 4.0 ng/mL. It remains to be determined whether the hypogonadal state is a risk factor for prostate cancer or whether smaller prostate volume allows for a more thorough evaluation with a fixed number of prostate biopsies.

Prostate Cancer Markers

Although PSA is, without a doubt, the most important tumor marker in human oncology, the quest for better markers continues. Two abstracts described uPM3, a new molecular assay for prostate cancer based on urine specimens.[39,40] The uPM3 test is a nucleic acid–based amplification assay that detects, in urine, expression of PSA mRNA, as a marker of prostate cells, and PCA3 mRNA, which is selectively expressed in the majority of prostate cancer patients. In both studies, which utilized different test populations, the uPM3 test offered significant enhancement of test performance over PSA measurement in historical series.

Tinzl and colleagues[39] analyzed 82 urine specimens with the uPM3 test. The cancer detection rate was 31%. uPM3 test sensitivity was 60% and, impressively, specificity was 81%. Saad and colleagues[40] evaluated 443 samples and found uMP3 sensitivity and specificity to be 67% and 89%, respectively. Furthermore, the investigators demonstrated a positive predictive value for uPM3 of 75% (vs 38% for PSA) and a negative predictive value of 84% (vs 81% for PSA). These data clearly demonstrate that uPM3 may emerge as an important new marker, particularly with respect to enhancing test specificity. For example, the finding of hematuria in a urine analysis, a highly sensitive but minimally specific test for urologic cancers, is followed up with a more specific test, such as imaging, cystoscopy, or markers of transitional cell carcinoma. The uPM3 test may offer an analogous opportunity for prostate cancer.

Veltri and associates[41] evaluated a derivative of fPSA (proPSA), which may be associated preferentially with prostate cancer, in a study of 93 men with tPSA levels between 4.0 ng/mL and 10.0 ng/mL. ProPSA, %fPSA, and tPSA were determined, and subjects underwent 12-core needle biopsy. Forty-four percent of the men were found to have prostate cancer. With univariate logistic regression, tPSA, fPSA, %fPSA, percent sum-proPSA, and prostate volume, all significantly differentiated men with or without cancer. With multivariate analysis, only tPSA, %fPSA, and sum-proPSA were retained. Utilizing 90% sensitivity levels, these 3 variables collectively demonstrated a specificity of 44% for the detection of prostate cancer.

Patient Monitoring

Choo and associates[42] evaluated the PSA doubling time (PSADT) in clinically localized, low-to-intermediate grade prostate adenocarcinoma managed with watchful waiting. Of 244 men who were evaluated, 229 had a minimum of 6 months of follow-up and 3 PSA determinations. In this cohort, median follow-up was 36 months and median frequency of PSA measurement was 8 times. Median PSADT was 9.3 years; 112 patients (49%) had PSADTs greater than 10 years. PSADT did not show any correlation with patient age, clinical stage, Gleason score, or initial PSA level. The investigators concluded that the PSADT in men being managed with watchful waiting varies widely and is not predicted by baseline variables.

Partin and associates[43] updated

the previously reported Johns Hopkins data regarding the natural history of progression to metastases after PSA elevation following radical prostatectomy. The study included 321 men with follow-up for an average of 10.57 ± 4 years. The median time from biochemical to metastatic progression was 7.5 years. The median actuarial time from development of metastases to death was 6.5 years. In the original study, time to biochemical recurrence (less than or greater than 2 years), PSADT within the first 2 years after recurrence (less than or greater than 10 months), and prostatectomy Gleason sum (5-7 vs 8-10) were significant indicators of progression, with specificities of 23%, 33%, and 15%, respectively. Although utilizing these 3 parameters provided significant enhancement in test specificity, the economic implications of such elaborate laboratory testing render the utility of such a strategy of questionable application.
[Michael K. Brawer, MD]

Prostate Cancer Highlights

Epidemiology

New data presented by Ornish and colleagues[44] demonstrate that lifestyle changes, including a low-fat diet and regular exercise, may slow, stop, or even reverse the progression of prostate cancer. This study represents the first randomized, controlled clinical trial of the effect of lifestyle changes on the progression of prostate cancer, as measured by PSA levels. Ninety men with histologically documented early prostate cancer who chose watchful waiting over conventional treatment (for reasons unrelated to the study) were randomized to an experimental group or a non-intervention control group. Subjects had PSA levels ranging from 4.0 ng/mL to 10.0 ng/mL and Gleason scores less than 7. Intervention included at least 3 hours of exercise a week for 30 minutes per session, a strict low-fat vegetarian diet, and a stress-management program that consisted of breathing techniques, meditation, gentle stretching, guided imagery, and progressive relaxation. PSA levels were measured twice at baseline and once every 3 months for 1 year.

At 3 months and 1 year, respectively, mean PSA levels decreased by 5% and 4% in the intervention group but rose by 1% and 6% in the control group. Overall adherence to the intervention program was 94% in the experimental group. However, 45% of those in the control group also adhered to the program for personal health reasons. Thus, differences in PSA levels would have been more dramatic if patients in the control group had not adhered to the intervention program. In addition, adherence to lifestyle changes correlated with inhibition of LNCaP prostate cancer cell growth by 70% in the intervention group and 9% in the control group. Testosterone levels, however, did not change significantly in either of the 2 groups. The authors concluded that their findings are clinically significant because prostate cancer is unlikely to metastasize in patients whose PSA levels are declining.

Lifestyle changes, including a low-fat diet and regular exercise, may slow, stop, or even reverse the progression of prostate cancer.

Prostate Cancer Detection and Screening

New forms of serum PSA comprise an uprising theme in prostate cancer research. Catalona and associates[45] presented data supporting proPSA as a useful tool for the detection of more aggressive prostate cancers in men with PSA levels in the 2.0 ng/mL to 4.0 ng/mL range. In receiver operating characteristic (ROC) area under the curve (AUC) analysis, proPSA yielded a specificity of 19% at 90% sensitivity, which was more accurate than fPSA, cPSA, or tPSA. ProPSA also outperformed the other PSA forms in distinguishing cancer Gleason score ($P = .002$). These findings indicate that proPSA may be the better screening tool and more likely to identify high-grade cancers.

Partin and colleagues[46] examined the clinical utility of proPSA (cancer PSA) and BPSA (benign PSA) when %fPSA is below 15%, an indication of a higher risk of cancer. Data regarding these new markers have suggested a benefit in early cancer detection, as seen in earlier studies of men with PSA levels in the low range. Sera of 161 men with %fPSA less than 15% were analyzed. Overall AUC-ROC for the group for tPSA and fPSA were 0.51 and 0.54, respectively. There was no statistically significant difference between proPSA and fPSA levels for diagnosis. Both BPSA and proPSA/BPSA significantly improved cancer detection over %fPSA ($P < .005$). In conclusion, the authors suggest that the ratio of proPSA and BPSA can distinguish cancer with greater accuracy when %fPSA is below 15%.

Seitz and colleagues[47] compared pathologic and biochemical features of cancers detected on first and repeat biopsies in men with PSA levels between 2.5 ng/mL and 4.0 ng/mL. In this prospective study, 315 men with tPSA levels of 2.5 ng/mL to 4.0 ng/mL underwent transrectal ultrasound (TRUS)–guided sextant biopsy and 2 additional transition zone biopsies. Subjects whose biopsy samples were negative for prostate cancer underwent

a repeat biopsy after 6 weeks. Cancer detection rates on first and second biopsy were 24% (75/315) and 13% (31/192), respectively. Of subjects with clinically localized prostate cancers, 87%, 11%, and 2% underwent radical prostatectomy, radiation therapy, and watchful waiting, respectively. Results showed no differences between cancers found on first or repeat biopsies with regard to extracapsular extension (P = .17), seminal vesicle invasion (P = .18), final pathologic stage (P = .3), Gleason score (P = .2), % Gleason grade 4/5 (P = .1), serum PSA, or age, suggesting identical cancer characteristics.

In a multicenter trial, Djavan and colleagues[48] validated a newly developed nomogram (Vienna nomogram) defining the optimal number of biopsy cores required for prostate cancer detection based on PSA level, patient age, and prostate volume. The cancer detection rate after the first set of biopsies was 38.1% with the Vienna nomogram (n = 394), compared with 22.8% with the standard octant biopsy protocol (n = 935), which represented a significant difference (P = .002, Fisher exact test). Early and delayed morbidity based on a patient questionnaire and registered morbidity at follow-up were also evaluated. Results showed significant reduction in hematuria (P = .006) in the Vienna nomogram group and no differences in rectal bleeding (P = .22), vasovagal episodes (P = .32), or urinary retention (P = .31). The investigators concluded that the Vienna nomogram is an easy-to-use tool that defines the optimal number of biopsy cores based on age and prostate volume and significantly improves prostate cancer detection.

Lowe and colleagues[49] conducted an important thought-provoking review of 233,989 biopsies to examine changing patterns of prostate biopsy techniques from 1997 to 2001. All biopsies submitted were reviewed and analyzed for diagnosis, patterns of biopsy, and cancer detection rate by year and by number of specimen containers. There has been a continual increase in the number of specimen containers submitted, with mean numbers of 4.7, 5.1, and 5.6 for 1997, 1999, and 2001, respectively. There has been a decrease in 1-, 2-, and 6-jar patterns with a simultaneous increase in 8-, 10-, and 12-jar patterns. Cancer detection rates were higher in multiple (7-13) jar patterns (34.3%-40.9%) than in 1-, 2-, and 3-jar patterns (28.3%-32.1%). In conclusion, biopsy techniques trend toward increasing the number of cores being taken as well as the number of site-specific containers being submitted, thus improving prostate cancer detection.

Prostate Cancer Staging

Strasser and associates[50] examined the use of 3-dimensional TRUS for staging of localized prostate cancer in 107 patients undergoing radical prostatectomy. Three-dimensional TRUS identified 62 of the 71 patients with extracapsular extension on final pathologic examination, corresponding with an 87% sensitivity, 94% specificity, and a 97% positive predictive value. Seminal vesicle invasion was correctly detected in 14 of 16 patients (88% sensitivity, 98% specificity, 98% positive predictive value). According to these data, three-dimensional TRUS, as a minimally invasive, easy-to-use, reproducible, and inexpensive examination tool, appears to be at least as accurate as endorectal MRI in preoperative staging of prostate cancer.

Little is known about the value of molecular forms of PSA for prostate cancer staging. To this end, Ghawidel and colleagues[51] evaluated the value of cPSA and cPSA indices, as well as %fPSA, PSAD, and PSATZ, for predicting the final pathologic stage. Sixty-nine (57%) of 121 subjects were found to have pathologically organ-confined prostate cancer, whereas 52 (43%) of 218 subjects were found to have extracapsular disease. cPSA levels were significantly higher in patients with extracapsular disease than in those with organ-confined cancers (4.84 ng/mL/cc vs 7.49 ng/mL/cc; P < .00001). Using multivariate analysis, cPSA, c/tPSA, and Gleason score were the most significant predictors of extracapsular disease. The AUC was larger for c/tPSA (0.825) and cPSA (0.794) than any other parameters. Cutoff points of 6.5 ng/mL/cc for cPSA level and 87% for c/tPSA ratio provided 88.1% and 92% specificity, respectively, and 20.8% and 27.4% sensitivity, respectively. Thus, these markers add significant benefit in predicting organ-confined disease or extracapsular extension.

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Haese and associates[52] validated a biopsy-based pathologic algorithm to predict lymph node metastases in clinically localized prostate cancers and evaluated its impact on selection of treatment modalities. Subjects were subdivided into 3 risk groups according to number of positive cores with Gleason grade 4 patterns. Of 443 patients, 20 had intraoperative lymph node metastases. The algorithm classified 404 patients to the low-risk group, 30 patients to the intermediate-risk group (≥ 1/6 cores with dominant

Gleason grade 4), and 9 patients to the high-risk group (≥ 4/6 cores with Gleason grade 4). The incidences of lymph node metastases were 2.47%, 20%, and 44.4% in the low-, intermediate-, and high-risk groups, respectively, with a negative predictive value for the low-risk group of 97.52%. The authors concluded that the Hamburg algorithm proved to be a valid tool for predicting lymphatic spread. As increasing numbers of patients undergo treatment options in which lymph node dissection is not performed, this algorithm provides important selection basis for the appropriate treatment.

Risk of PSA recurrence increased with baseline PSA level (P < .0001), Gleason score (P = .0513), and pathologic stage (P < .0001).

An interesting study by Remzi and colleagues[53] focused on color Doppler TRUS, time to recurrence, and PSA density to replace biopsy in detecting local recurrence following radical prostatectomy. The purpose of the study was to evaluate a new protocol for the accurate prediction of early local recurrent cancer in a biopsy-controlled study. Biopsy of the anastomotic region was obtained for 149 patients with biochemical recurrence (10-79 months, mean 23 months) after radical prostatectomy. Cancer was detected in 51 patients (34%), whereas benign prostatic and fibrotic tissue were found in 16 (11%) and 82 (55%) patients, respectively. Perfusion characteristics differed in terms of quality and quantity, with the strongest signals for recurrent cancer. Color Doppler TRUS had a sensitivity and specificity of 84.6% and 92.4% (AUC = 89%), respectively, in predicting local recurrence and was, therefore, the most powerful predictor compared with time to recurrence (P = .002) and PSADT (P = .001).

In a similar study, Anagnostou and colleagues[54] examined biochemical recurrence due to residual benign prostatic tissue after radical prostatectomy and the need for anastomotic biopsies. Sixty-four patients with postoperative biochemical recurrence participated in the study; all subjects received a computed tomographic scan, bone scan, and TRUS-guided biopsy of the anastomotic region. Mean PSA value was 1.6 ng/mL (0.7-2.4 ng/mL), and median follow-up was 15.1 months (6-32 months). Benign prostatic tissue was found in 16 patients (25%), whereas prostate cancer was detected in 18 patients (28%). In conclusion, local recurrence after radical prostatectomy is difficult to assess with 1-time biopsy. There are, however, a variety of pathologic findings in TRUS-guided biopsies taken from the anastomotic region, and the incidence of benign tissue in cases of biochemical failure justifies biopsy in these patients.

Treatment

Stone and associates[55] reported on 10-year biochemical and local control results for real-time I-125 prostate brachytherapy in 279 men followed for at least 4 years. Median patient age was 67 years. Initial PSA level (median, 7 ng/mL) was 10 ng/mL or lower in 202 patients and higher than 10 ng/mL in 77 patients. Gleason score was 6 or lower in 97.5% of subjects; 71% had a staging of T2a or lower. One hundred forty-six subjects were classified as low-risk patients. Median follow-up was 6 years. Multivariate analysis identified D90 dose (P < .001) and risk group (P < .01) as the only significant variables. The risks of PSA failure (risk ratio 95%) were 5.4 (P = .002) and 9.3 (P < .001) for D90 doses below 140 Gy and 120 Gy, respectively. Biochemical freedom from failure was as high as 85% for patients with negative prostate biopsies (166/185), compared with 21% for those with positive biopsies (P < .001). Biopsy was positive in 4.6% of the patients with a D90 dose of at least 160 Gy, compared with 13.6% of those with a lesser dose (P < .001). From these data, the investigators concluded that risk category and delivered radiation dose are important predictors of success of real-time I-125 prostate brachytherapy. They also stressed the importance of achieving a radiation dose of 160 Gy.

Gleave and colleagues[56] presented the results of a phase III trial conducted to compare the effects of 3 months and 8 months of neoadjuvant hormone in reducing PSA recurrence rates after radical prostatectomy. A total of 549 patients were divided into 2 groups that were equally stratified for T-stage, Gleason grade, and baseline PSA level. Pre-surgery PSA nadir levels (P < .001) and positive margins (P = .0106) were significantly lower in the 8-month treatment group. Overall PSA recurrence rate was 24.5%, with no significant difference between the 2 groups (25.4% vs 23.6% in the 3- and 8-month groups, respectively). Risk of PSA recurrence increased with baseline PSA level (P < .0001), Gleason score (P = .0513), and pathologic stage (P < .0001). Kaplan-Meier subgroup analysis showed no trend toward delay in time to biochemical recurrence in the 8-month treatment group (P = .0511), and no significant difference in PSA recurrence rates was observed with longer duration neoadjuvant hormone therapy at 3 years post-surgery.

Krygiel and colleagues[57] presented results of a comparative study of radical prostatectomy, radiotherapy, hormonal therapy, and watchful waiting

for screen-detected prostate cancer. With 4 additional years of data, this report follows up on a cohort study that followed 2725 patients diagnosed with prostate cancer. The results were similar to prior data that demonstrated radical prostatectomy to provide a better 7-year progression-free survival than the other methods. The percentages of patients who progressed in the radical prostatectomy, radiotherapy, hormonal therapy, and watchful waiting groups were 16%, 24%, 41%, and 54%, respectively; 7-year progression-free survival rates were 82%, 67%, 64%, and 35%, respectively. Nevertheless, early detection of aggressive cancers in younger men remains a primary goal of oncologic urology.

Basic Research

A study by Rusthoven and associates[58] described a new and highly accurate method of determining chromosome 8p loss called counting alleles. This methodology uses colored fluorescent probes as molecular beacons on DNA to accurately determine single nucleotide polymorphisms, allowing a more accurate assessment of 8p loss. This technique was employed in a large population of men receiving long-term follow-up after radical prostatectomy. Results showed that the combination of surgical margin and 8p loss was highly predictive of clinical recurrence of prostate cancer. Sixty-four percent of the patients informative for 8p had allelic imbalance. Among the subjects with allelic imbalance, 65% had Gleason scores of 7 or greater, compared with 37% of subjects with allelic retention ($P < .001$). Loss of 8p also correlated with extracapsular extension ($P < .01$) and seminal vesicle invasion ($P < .001$). Clinical recurrence was seen in 53% of patients with positive surgical margins, compared with 17% of patients with negative surgical margins. Sixty-seven percent of subjects who had both chromosome 8p loss and positive surgical margins showed clinical recurrence; only 4% of patients who had chromosome 8p loss and negative surgical margins showed clinical recurrence ($P < .000001$). This technique may, therefore, allow for the selection of post–radical prostatectomy patients who may most benefit from adjuvant treatment, such as radiation therapy.

Patients with a homozygous T genotype in the hk2 *gene had an essentially 4-fold greater risk of a subsequent positive biopsy.*

In another study, Nam and associates[59] examined the role of serum human kallikrein-2 (hk2) protein levels and a genetic polymorphism (T for C substitution) at the *hk2* gene in predicting subsequent positive biopsies. Serum hk2 and *hk2* genetic polymorphism were determined for a series of 1287 patients. Of these men, 616 patients had cancer on biopsy and 671 had no cancer (controls). Analysis demonstrated that patients with a homozygous T genotype in the *hk2* gene had an essentially 4-fold greater risk of a subsequent positive biopsy. If patients had elevated serum levels of hk2 protein and at least 1 T allele, the relative risk was nearly 14-fold.

Racial Differences

Japanese men have a lower incidence of prostate cancer and experience better outcomes from the disease than do American men. A study by Marks and colleagues[60] concluded that these lower rates and better outcomes are a result of diets higher in soy and lower in animal fat. To factor out genetic causes, the study included 25 Japanese men living in Japan and 25 men of Japanese descent living in the Los Angeles area; therefore all subjects had the same genetic background but different diets, namely, higher intakes of soy in Japan and higher intakes of animal fat in the United States. Both groups of men had prostate cancer treated with radical prostatectomy, and prostate tissue samples were analyzed. Tissue analyses found that the native Japanese men had higher concentrations of caspase-3, an apoptotic mediator that is a biomarker for lower frequency of disease and increased survival from prostate cancer. Results also suggested that differences in DNA may indicate a gene-nutrient interaction to be responsible for the differences in prostate cancer frequency and outcomes.

Roehrborn and associates[61] analyzed baseline data from the phase III dutasteride trials regarding racial differences in prostate volume and serum PSA measurements. The study included 4250 patients (white [n = 3961], black [n = 161], Hispanic [n = 128]) who had a total prostate volume of 30 mL or greater and a tPSA level between 1.5 ng/mL and 10 ng/mL. There were no differences among the racial groups with respect to International Prostate Symptom Score (IPSS) or peak flow rate. Black patients had larger transition zones (not significant) but similar total prostate volumes and, thus, their transition zone indexes were higher (not significant). tPSA levels were higher in black subjects compared with white and Hispanic subjects, but fPSA levels and f/t PSA ratios were not significantly different. The authors concluded that, in men of similar age who are experiencing the same problems of lower urinary tract symptoms (LUTS) and reduced flow rate, black

men have larger transition zone volumes and transition zone indexes, as well as higher tPSA levels, but similar total prostate volumes and fPSA levels.

Advanced Prostate Cancer

J591 is a recently developed monoclonal antibody that targets the extracellular domain of prostate-specific membrane antigen. A noteworthy study by Trabulsi and colleagues[62] evaluated the use of J591 radiolabeled with Yttrium[90] or Lutetium[177] in patients with advanced prostate cancer. Of the 53 evaluable patients, 36% had failed at least 1 chemotherapy regimen. Bone metastases and soft tissue disease were observed in 72% and 44% of subjects, respectively. Every visible lesion was successfully targeted. Toxicity was dose-related and limited to reversible myelosuppression. Results showed disease shrinkage of greater than 90%, and a decrease in PSA of up to 85%. It seems that this antibody, when tagged, is appropriate for both diagnosis and treatment of advanced prostate cancer. The investigators concluded that J591 targets tumor sites with high sensitivity and specificity and that toxicity is limited to dose-related, reversible myelosuppression related to the radioactivity.

J591, when tagged, is appropriate for both diagnosis and treatment of advanced prostate cancer.

Although radiotherapy is used as a curative treatment of prostate cancer, locally persistent cancer is found in a large proportion of patients. Therefore, Ward and associates[63] analyzed outcomes and complications from a 30-year experience of salvage prostatectomy for radiorecurrent prostate cancer. The analysis included 199 patients, and mean follow-up was 7 years. Bladder neck contracture (22%) and urinary extravasation (15%) were the most common postoperative complications. Continence improved from 43% to 56%, with an additional 20% of patients requiring 2 or fewer pads per day. Patients with cancers amenable to radical prostatectomy had a median progression-free survival of 8.7 years.

Serenoa repens

Phytotherapy has been shown to be beneficial in the conservative management of benign prostatic hyperplasia (BPH). Hruby and associates[64] conducted a prospective study comparing the results of phytotherapy, placebo, and watchful waiting on delay of disease progression in 191 men with mild symptoms of bladder outlet obstruction (BOO) (IPSS < 8). At 6, 12, 18, and 24 months, cumulative progression rates were 1%, 7%, 9%, and 16%, respectively, for the patients who received *Serenoa repens* therapy and 6%, 13%, 15%, and 24%, respectively, for the matched group who received watchful waiting. Progression rates were significantly higher (P = .001) when artificial neural network calculated cutoffs for progression were used (PSA > 1.5 ng/mL, transition zone volume > 25 cc). Progression rates were significantly lower in the *Serenoa repens* group compared with those of earlier matched patients who received placebo (P = .003). IPSS, quality of life, and maximum flow rate improved by 17%, 19%, and 15%, respectively, in the *Serenoa repens* cohort versus 6%, 9%, and 10%, respectively, in the watchful waiting cohort. In conclusion, progression rates in men with mild symptoms of BOO who received *Serenoa repens* were significantly reduced compared with those of patients who received watchful waiting and those of a matched group of patients who received placebo.

BPH: New Technology

TUMT has gained respect as a treatment modality for BPH. Huidobro and associates[65] reported data on use of a new catheter, the Cooled ThermoCath™ (CTC; Urologix, Inc), for treatment of BPH. This catheter utilizes a new cooling system that allows a high-temperature 28.5-minute treatment intended to cause necrosis and treatment efficacy similar to the Targis® 60-minute, with the same or better comfort for the patient. AUA symptom scores for the CTC 28.5-minute group at baseline, 6 months, and 12 months post-treatment were 20.9, 5.6, and 6.9, respectively, compared with 21.0, 8.3, and 8.4, respectively, for the Targis 60-minute group. Peak flow rates for the CTC group were 9.8 mL/s, 12.7 mL/s, and 12.7 mL/s, respectively, compared with 8.7 mL/s, 13.7 mL/s, and 14.0 mL/s, respectively, for the Targis group. Quality-of-life scores were 4.9, 0.8, and 1.6, respectively, for the CTC group, and 4.1, 1.4, and 1.6, respectively, for the Targis group (Table 1). These data indicate that CTC 28.5-minute provides similar or improved patient comfort and comparable necrosis sites at 1 week. Nevertheless, more long-term data are needed to confirm these early benefits.

Seitz and associates[66] conducted a prospective, nonrandomized, 3-year study on high-energy TUMT and adjuvant α-blockade in 32 men with category IIIB CP/CPPS. Mild improvements in subjective global assessment (SGA) and NIH CPSI was observed in 75% and 92% of patients, respectively, at 1 year; 69% and 78% of patients, respectively, at 2 years; and 67% and 77% of patients, respectively, at

Table 1
Cooled ThermoCath 28.5-Minute Versus Targis 60-Minute as Therapy for Benign Prostatic Hyperplasia

	Cooled ThermoCath 28.5-Minute			Targis 60-Minute		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
AUA symptom score	20.9	5.6	6.9	21.0	8.3	8.4
Peak flow rate, mL/s	9.8	12.7	12.7	8.7	13.7	14.0
QoL score	4.9	0.8	1.6	4.1	1.4	1.6

AUA, American Urological Association; QoL, quality of life.
Data from Huidobro et al.[65]

3 years. Marked improvements in these indices were seen in 55% and 60% of patients, respectively, at 1 year; 49% and 51% of patients, respectively, at 2 years; and 48% and 49% of patients, respectively, at 3 years. The improvements in SGA and CPSI suggest that high-energy TUMT provides a significant clinical benefit to patients with IIIB prostatitis. Adjuvant α-blockers enhance TRUS efficacy and, therefore, the combination of these therapies might be used in patients who have failed medical therapy. This treatment does, however, require sedoanalgesia.
[Michael Dobrovits, MD, Mesut Remzi, MD, Bob Djavan, MD, PhD]

Medical Therapy for LUTS and BPH

Once again, the topics of LUTS and BPH received a great deal of attention at this year's annual meeting of the AUA. Forty-four posters regarding basic research in BPH were presented; 20 posters were presented in a session on the natural history and epidemiology of the condition; 32 presentations were made in podium and poster sessions on medical and hormonal therapy; and 32 presentations, also divided into podium and poster sessions, were made regarding surgical therapy and new technologies for BPH. During 2 morning plenary sessions, state-of-the-art updates on the medical management of BPH (Steven Kaplan, MD) and minimally invasive surgical therapy (MIST Interventions) for BPH were presented—evidence of the significant interest in these topics. The latter topic was discussed by a panel of experts (moderator: Reginald Bruskewitz, MD; panelists: Claus Roehrborn, MD; Kevin McVary, MD; Christopher M. Dixon, MD).

BPH: Medical and Hormonal Therapy
The Medical Therapy of Prostatic Symptoms (MTOPS) trial, which was introduced at last year's meeting, received significant attention, and several MTOPS analyses were presented in both podium and poster sessions. At present, the MTOPS trial is the longest and largest trial ever conducted for LUTS and BPH. Funded by the National Institute of Diabetes & Digestive & Kidney Diseases, the trial enrolled 3047 men with a median baseline age of 62 years, a baseline AUA symptom score of 17 points, and a peak urinary flow rate of 10.6 mL/s. Prostate volume at baseline was 31 mL, and serum PSA level was 1.6 ng/mL. Subjects were randomized into 4 treatment groups: placebo; the 5-α-reductase inhibitor finasteride at a dosage of 5 mg daily; the α-adrenergic receptor blocker doxazosin, titrated to response to either 4 mg or 8 mg; or a combination of finasteride, 5 mg, and doxazosin, 4 mg or 8 mg, daily. Overall trial results were presented last year and were received with great interest by the audience at the AUA meeting and, later, by worldwide audiences. Although still under review, the manuscript has been submitted for publication later this year in the *New England Journal of Medicine.*

The first presentation of the podium session asked the question of whether baseline measures can predict the risk of BPH progression in placebo-treated patients.[67] A total of 737 men were randomized to placebo and followed for an average of 4.5 years. Univariate regression models were established to determine whether progression to invasive therapy for BPH, acute urinary retention (AUR), symptomatic progression by 4 or more points on the symptom score, or overall progression (a combined end point including symptomatic progression, socially unacceptable incontinence, recurrent urinary tract infections by urosepsis, renal insufficiency, or AUR) could be predicted based on several baseline parameters. In an initial cut of the data, the absolute risk of BPH events was cal-

Improvements in SGA and CPSI suggest that high-energy TUMT provides a significant clinical benefit to patients with IIIB prostatitis.

culated by stratifying the placebo-treated patients based on the median value of each baseline parameter. Baseline age proved to be a highly significant predictor of overall disease progression (3.5/100 person-years [PY] vs 5.2/100 PY for patients aged 62 years or older). Baseline age also significantly predicted symptomatic progression, which accounted for 3 of 4 progression events.

Subjects with PSA levels below the median of 1.6 ng/mL had much reduced risks of overall progression, symptomatic progression, AUR, and progression to invasive therapy, compared with the 50% of subjects who had PSA levels above the median. Overall disease progression for subjects in the below-median PSA group was 3.1/100 PY versus 5.9/100 PY for those in the above-median group. The data were relatively similar for TRUS-estimated prostate volumes, for which the mean value was 31 mL.

The Proscar Long-Term Efficacy and Safety Study (PLESS) had already documented PSA level and prostate volume as significant predictors of progression to AUR and/or invasive therapy for BPH.[68] However, data from MTOPS showed that the objective baseline parameters of serum PSA level and TRUS-measured prostate volume can predict progression of a subjective end point, such as symptomatic worsening. In addition, peak urinary flow rate at baseline was shown to be predictive of overall and symptomatic progression, as well as progression to invasive therapy. For example, patients with a maximum flow rate below the median of 10.6 mL/s had a rate of symptomatic progression of 4.9/100 PY, whereas those with a maximum flow rate above the median had a rate of only 2.4/100 PY. Even post-void residual urine, which in the past had only been considered of marginal value in the evaluation and follow-up of patients with BPH, proved to be a significant predictor of overall progression, symptomatic progression, and progression to invasive therapy.

The results observed in the placebo group of the MTOPS study are of critical importance to physicians who counsel men with LUTS and BPH.

Baseline age proved to be a highly significant predictor of overall disease progression.

Prior studies, such as the aforementioned PLESS trial,[68] had verified that baseline TRUS volume and PSA level are predictive of progression to AUR and surgery. However, no prior trial had attempted to correlate subjective outcomes, such as symptomatic worsening, to objective baseline parameters. The MTOPS trial clearly demonstrates that prostate size and, as a proxy parameter of prostate size, serum PSA level at baseline are highly predictive of symptomatic worsening and progression, thereby establishing a correlation between an objective measurable parameter at baseline and change in a subjective parameter—namely, symptom score—over time.

Another presentation also focused on the placebo-treated patients in the MTOPS trial and the observed changes in prostate volume over time.[69] The PLESS study had established that serum PSA level may be a powerful predictor of future prostate growth.[68] Initial analysis of data from the MTOPS trial revealed that patients who received placebo and those who received doxazosin had virtually identical increases in prostate volume over time, both in absolute and percentage terms. Thus, the 2 patient cohorts were combined, and a per-protocol analysis of 1148 patients was performed.

In the combined group, the unadjusted mean change in total prostate volume from baseline was 9.3 ± 13.2 mL, resulting in an unadjusted mean percentage change from baseline of 29.3 ± 36.3%. When stratified by PSA quartiles, the increase in total prostate volume in the lowest quartile was 4.9 mL (24.9%), compared with 16.2 mL (34.5%) in the highest quartile; these data represent an annualized growth rate of 1.5 mL/y versus 3.6 mL/y in the lowest and highest PSA quartiles, respectively. Transition zone volume, which was not assessed in the PLESS trial, was also measured. Transition zone volume increased 1.7 mL (34.3%) in the lowest PSA quartile and 9.3 mL (49.2%) in the highest PSA quartile, for an annualized growth rate ranging from 0.4 mL/y to 2.1 mL/y. Whereas baseline total and transition zone volume increased with age, absolute or percent changes of volume over time did not correlate with age.

Peak urinary flow rate at baseline was shown to be predictive of overall and symptomatic progression, as well as progression to invasive therapy.

These 2 presentations, which focused entirely on the MTOPS subjects in the placebo group and, in the latter case, the doxazosin-treated group, verify that serum PSA level is indeed a useful clinical predictor of the natural history of BPH in terms of future prostate growth, sympto-

matic worsening, progression to urinary retention, and progression to invasive surgery.

A third MTOPS presentation focused on the question of whether baseline parameters can predict clinical progression in the medically treated arms of the trial.[70] Patients were again stratified by median age, PSA level, TRUS volume, peak urinary flow rate, and post-void residual urine. Hazard ratio analysis showed that a higher age at baseline confers a significantly greater risk of BPH progression in all medically treated groups. A higher serum PSA level, larger prostate volume, or reduced urinary flow rate proved to be significant predictors in the doxazosin-treated patients only. These results indicate that, in patients who received finasteride or combination therapy, the stratifying parameters of serum PSA level and prostate volume became irrelevant, that is, patients with lower or higher PSA levels or larger or smaller prostate volumes had a similar risk of overall disease progression. A univariate regression of risk versus these covariants demonstrated that a PSA level higher than 1.6 ng/mL (median) at baseline is predictive of overall and symptomatic progression of BPH in the doxazosin-treated patients, AUR in all treatment groups, and invasive therapy for BPH in the doxazosin and combination groups.

A retrospective analysis corroborated the findings of the MTOPS study regarding the relationship between baseline serum PSA level and subjective disease progression in terms of symptom worsening. The Prospective European Doxazosin and Combination Therapy (PREDICT) trial, a 1-year trial conducted in Europe, randomized more than 1000 patients to placebo, doxazosin, finasteride, or combination therapy. Although symptomatic worsening was not a defined end point of the trial, a retrospective analysis was performed to determine the percentage of patients who experienced a worsening of 3, 4, or 5 points on the IPSS during the course of the trial.[71,72]

Post-hoc analysis showed median PSA level to be a powerful stratifier of subjects in the placebo group. Among subjects who received placebo, a worsening in IPSS of 3 or more points was observed in 12% and 21% of those with baseline PSA levels less than 2 ng/mL and greater than 2 ng/mL, respectively; IPSS worsened by 4 or more points in 12% versus 16%, and by 5 or more points in 9% versus 13.4%, of subjects with PSA levels less than 2 ng/mL versus greater than 2 ng/mL, respectively. Patients who received doxazosin had a significantly reduced probability of symptomatic progression provided their PSA level was less than 2 ng/mL. In subjects who had a PSA level higher than 2 ng/mL, combination therapy was most effective. The probabilities for a 3-, 4-, or 5-point or more worsening in IPSS were 5.0%, 4.3%, and 3.6% in the combination-therapy group versus the aforementioned 12%, 12%, and 9% in the placebo group, respectively. This represents a greater than 50% reduction in risk of progression, independent of the threshold chosen.

LUTS and Sexual Dysfunction

It had been suggested in the past that there is a correlation between increasing severity of LUTS in aging men and decreasing sexual function and satisfaction. Only recently, however, have significant data sets emerged that lend credence to this hypothesis. The MTOPS study provided baseline data that demonstrate a correlation among age, LUTS, and sexual dysfunction as measured in 5 domains.[73] When subjects were stratified into quartiles by baseline symptom score (8-11 points, 12-16 points, 17-20 points, 21-30 points), LUTS were significantly related to worsening of sexual drive, sexual function, ejaculatory function, the patient's assessment of his sexual problems, and overall satisfaction with sexual functioning. Of interest, when subjects were stratified into quartiles by baseline prostate volume, significant relationships were again observed, with patients with larger prostate volumes having less sexual drive, lower overall sexual functioning, decreased ejaculation function, and increased sexual problems. Similar observations were made regarding transition zone volume.

The correlation of LUTS with difficulty achieving an erection and level of sexual drive decreased with age but remained significant within all age decades.

In 1989, an age-stratified, random sample of 2015 white men aged 40 to 79 years who had not had prostate surgery, prostate cancer, or any other conditions that affect voiding function (except BPH) were enrolled in the Olmsted County Study of Urinary Symptoms and Health Status in Men.[74] Patients were asked about symptom severity, as well as 12 validated questions regarding sexual functioning. Results showed that all sexual domains were inversely related to the severity of LUTS, with Spearman correlation coefficients ranging from –0.15 to –0.30 in those 5941 men who reported having regular sexual partners. The correlation of LUTS with difficulty achieving an erection and level of sexual drive decreased with age but remained significant within all age decades. Difficulty achieving an erection had

the strongest association with LUTS.

Another group of investigators presented data on 3230 men with LUTS from Europe, Russia, the Middle East, Latin America, and Asia.[75] Patients with severe LUTS were found to be twice as likely to experience erectile dysfunction (ED) and a reduced ejaculate volume compared with those with mild-to-moderate LUTS.

These large-scale, cross-sectional, longitudinal epidemiologic observations strongly suggest that, indeed, LUTS in aging men correlate with various domains of sexual dysfunction. Patients presenting with either sexual dysfunction or LUTS should be screened for the presence of associated symptomatology.

Other Trials

It had been demonstrated that α-adrenergic receptor blockers given at the time of AUR may increase the chance of a successful trial without a catheter (TWOC) and allow patients to resume normal urination. Hargreave and colleagues[76] presented data from a randomized, placebo-controlled trial of the α-blocker alfuzosin, 10 mg once daily, in patients presenting with an episode of AUR. The trial was divided into 2 phases. In the first phase of the trial, patients presenting with an episode of AUR were randomized to receive either placebo or alfuzosin. In the second phase, alfuzosin was analyzed for its effect on the prevention of recurrence of AUR or the need for BPH-related surgery following a successful TWOC. Phase 1 data from 363 patients were presented.

Treatment with alfuzosin significantly improved the likelihood of a successful TWOC from 47.9% in the placebo group to 61.9% in the alfuzosin group (P = .012). In a multivariate risk factor analysis, increasing age and retention volume reduced the likelihood of a successful TWOC, whereas treatment with alfuzosin doubled the likelihood of a successful TWOC. Similar data from a smaller study had previously been presented for the α-blocker tamsulosin, given at a daily dose of 0.4 mg.[77]

Data were also presented for the new 5-α-reductase inhibitor dutasteride, the first drug to inhibit both isoenzymes of 5-α-reductase. The phase III trial included 3 simultaneously conducted, randomized, placebo-controlled studies that enrolled nearly 4500 subjects.[78] Of 2802 patients originally randomized in 2 of these trials, nearly 1100 completed a 48-month open-label extension in which all patients were converted to treatment with dutasteride, 0.5 mg, after the conclusion of the 2-year double-blind phase.[79] After conversion to open-label dutasteride, the subjects who had previously received placebo experienced symptomatic improvement similar to that of the patients who had received dutasteride for 2 years. Of interest, the patients who received dutasteride for 2 years in the randomized, placebo-controlled phase of the trial had an approximate 4-point improvement in symptom score; they experienced an additional 2.1-point improvement in symptom score during the open-label extension for a total improvement of 6.1 points. A similar observation was made regarding maximum urinary flow rate: after an initial improvement of 2.3 mL/s at the end of 24 months, an additional improvement of 0.4 mL/s occurred during the open-label extension, for a total improvement of approximately 2.8 mL/s. The rates of AUR and surgery remained low during the open-label extension trial: accrued 48-month incidence of AUR was 2.2%, and accrued rate of surgery was 2.1%.

Although analysis by individual baseline parameters regarding the risk of symptomatic progression and progression to retention or surgery is of great interest, multivariate models that take into account several baseline parameters at the same time would be more useful. Two such promising efforts were presented at this year's AUA.[80,81] The 2 groups utilized different approaches. Boyle and colleagues[80] analyzed 2-year data from the 4325 patients enrolled in the multicenter placebo-controlled dutasteride studies. They used a statistical model analogous to the Gail model to predict breast cancer. The incidence of AUR was 4.2%. All variables were divided into 5 equal groups (quintiles). The risk of AUR was independently associated with peak flow rate, prostate volume, and baseline PSA level. The risks of AUR by baseline PSA quintile, in ascending order, were 1.0%, 1.2%, 2.5%, 3.9%, and 6.3%; this represented a highly significant trend. There was no association between risk of AUR and either age or baseline symptom score. A multidimensional model was developed that allows the physician to enter baseline parameters and provide the patient with a precise idea as to his risk of AUR over a defined time horizon.

The risk of AUR was independently associated with peak flow rate, prostate volume, and baseline PSA level.

Kattan and colleagues[81] also used the data from the phase III dutasteride trials to develop a nomogram. This nomogram differed in that it factored into account treatment with placebo or dutasteride. Cox proportional hazards regression was used to relate the baseline variables to the future probability of AUR over a 2-year period

Table 2
Cox Proportional Hazards Regression Results

Variable	*P* Value	Hazard Ratio	Hazard Ratio 95% CI
AUA-SI	.141	1.17	0.95-1.45
BII	.008	1.35	1.08-1.68
Prior α-blockers	.001	1.55	1.20-2.09
Prostate volume, cc	.001	1.29	1.15-1.45
PSA, ng/mL	.002	1.35	1.12-1.62
Qmax, mL/s	.001	0.60	0.50-0.73
Dutasteride therapy	.001	0.50	0.37-0.66

AUA-SI, American Urological Association Symptom Index; BII, benign prostatic hyperplasia impact index; PSA, prostate-specific antigen; Qmax, maximum flow rate.
Data from Kattan et al.[81]

(Table 2), and the nomogram was internally validated. The nomogram appears to be accurately calibrated and discriminating for the prediction of the probability of a patient to experience AUR or require surgical intervention with relative position.

Summary

This year's AUA provided new and exciting insights into the natural history of LUTS and BPH, the powerful and important role that baseline parameters play in predicting such risks, the ability of various medical interventions to prevent symptomatic progression as well as progression to AUR or surgery, and the relationship between LUTS and sexual dysfunction. Because there are several baseline parameters that are predictive of progression, efforts such as those presented by Boyle and colleagues[80] and Kattan and colleagues[81] point the way to the future.

Development of prediction models or nomograms incorporating data from several large-scale trials may allow physicians to predict the risks of symptomatic progression and/or progression to AUR or surgery for patients presenting with LUTS and BPH and, thus, to appropriately advise patients regarding therapeutic options. Furthermore, medical therapies could be chosen based on an individual risk assessment and/or the ability of these therapies to reduce such risks. A combination of various large data sets, such as those from the PLESS trial, the dutasteride trials, the MTOPS trial, and the Olmsted County study, is likely to allow for the formulation of such prediction models and nomograms.

[Claus G. Roehrborn, MD, FACS]

Male Infertility

Forty percent of diagnosed cases of male factor infertility can be traced back to a varicocele. Although varicocele repair remains an important treatment option in men with this condition, limited prospective data exist regarding its impact on pregnancy rates. At this year's annual meeting of the AUA, Dohle and colleagues[82] presented the results of a prospective, randomized study comparing varicocele repair versus watchful waiting among 61 couples with documented infertility of at least 1-year duration. In all couples, the varicocele was the only detectable cause of male infertility; all female partners tested normal in their ability to conceive.

After 1 year of observation, the pregnancy rate achieved in 31 couples randomized to male-partner varicocele repair was compared with that in 30 couples randomized to watchful waiting. Couples in the varicocele-repair group achieved a 36% pregnancy rate compared with 9% among couples in the control group. Of note, sperm concentration roughly tripled in men with corrected varicoceles versus no change in men who did not undergo the procedure. This study supports varicocele repair as an important consideration for couples attempting to conceive. At a time when couples are often encouraged to consider expensive and technologically complex procedures such as in vitro fertilization, rather than the correction of underlying male fertility factors, this finding is especially important.

Sperm concentration roughly tripled in men with corrected varicoceles versus no change in men who did not undergo the procedure.

As couples seek to delay pregnancy in deference to professional and personal goals, the effect of age on female fertility has received increasing attention. This factor is frequently an issue among couples considering vasectomy reversal. Kolettis and colleagues[83] reported on pregnancy rates following vasectomy reversal for couples in which the female partner was older than 35 years; the mean age of female partners was 37 years. Among 27 such couples, the live

delivery rate was 32%. The median obstructive interval among the men in the study was 10 years, and the post-reversal patency rate was 81%. For couples in which the female partner was older than 40 years, only 1 (8%) of 13 achieved a live delivery. The authors concluded that vasectomy reversal for couples in which the female partner is aged 35 to 40 years is associated with a reasonable chance of success.

Another important factor in the success of vasectomy reversal is the time elapsed between performance of the vasectomy and its reversal. An additional potential factor is the presence or absence of a sperm granuloma. Boorjian and associates[84] assessed the effects of both of these variables on 213 vasectomy reversals. Obstructive intervals were divided into 4 categories: less than 5 years, 5 years to 10 years, 10 years to 15 years, and longer than 15 years. Patency (defined as intact sperm in the semen) did not change as a function of obstructive interval (92%, 88%, 91%, and 89%, respectively). There was no difference in pregnancy rates among partners of patients in the lower 3 time intervals (90%, 82%, and 85%, respectively). However, subjects who had time intervals between vasectomy and reversal that were longer than 15 years had a significantly lower rate of pregnancy (44%; $P < .05$). Men with a sperm granuloma on at least one side achieved a 95% patency rate, compared with 78% for men with no palpable sperm granuloma ($P = .07$). Pregnancy rate was not affected by the presence or absence of sperm granuloma.

The authors concluded that patency rates achieved following vasectomy reversal were high among patients in all categories of obstructive interval. Moreover, pregnancy rates following vasectomy reversal among men in whom the obstructive interval was 15 years or less compared favorably with rates achieved with in vitro technologies. Even in men with obstructive intervals longer than 15 years, pregnancy rates were comparable or superior to those achieved using in vitro technologies.
[Randall B. Meacham, MD]

Impotence and Peyronie's Disease

At the 2003 meeting of the AUA, a number of interesting clinical and scientific presentations introduced novel data and shed light on some lingering dilemmas in the fields of impotence and Peyronie's disease.

Impotence

It is generally accepted that the most common cause of ED is "venous leakage" or failure to store, a condition in which the erection is not maintained long enough for the patient's satisfaction. Current thinking is that this condition is the result of smooth muscle cell (SMC) myopathy caused by aging and/or a physiologic insult, for example, diabetes, drug therapy, or hyperlipidemia. In a Belgium study, by Wespes and colleagues,[85] of men with ED who had failed sildenafil (Viagra®, Pfizer Inc, New York), 28 (90%) of 30 subjects did not respond to intracorporeal injection therapy; 24 (86%) of these 28 men had venous leakage as either their only problem (19 of 28 men) or in combination with arterial disease (5 of 28 men). All 30 patients who did not respond to sildenafil had a marked reduction in their SMC content as determined by penile biopsy. These results confirm that SMC dysfunction is the most common cause of ED in this selected population and that our attention in treating or preventing ED should focus primarily on SMCs.

Hellstrom and colleagues,[86] from Tulane, presented interesting data regarding the effect of tadalafil on sperm function in men. Because tadalafil has a high affinity for phosphodiesterase (PDE) 11 compared with other PDE inhibitors, and because PDE 11 is found primarily in the testes, there has been concern regarding the effect of PDE-11 inhibition on sperm parameters. The investigators showed that daily administration of tadalafil (10 mg or 20 mg) for 6 months did not affect sperm parameters that are currently used in clinical practice. This study is intriguing for another reason: continuous 24-hour PDE inhibition throughout the body with this PDE-5 inhibitor, which has a half life of almost 18 hours, did not seem to affect patients in any adverse way other than the normal side effects seen with any PDE-5 inhibitor. The time may come when continuous PDE inhibition may be used for a variety of disorders that may be better treated with this method than with intermittent inhibition.

Daily administration of tadalafil (10 mg or 20 mg) for 6 months did not affect sperm parameters that are currently used in clinical practice.

Another thought-provoking study examined the role of testosterone therapy for men with low testosterone levels who do not respond to sildenafil therapy.[87] The basis of this study was the observation that testosterone is responsible for the production of nitric oxide (NO) in the penile nerves; more specifically, the pathway appears to be dihydrotestosterone-dependent. The authors theorized that a decreased production of NO in men with low testosterone levels impacts the formation of cyclic guanosine monophosphate by guanylyl cyclase

and, therefore, drugs such as sildenafil cannot achieve optimum efficacy. Study results showed improved outcomes for men with low testosterone levels who received both testosterone and sildenafil, compared with those who received sildenafil alone. Results of this study suggest that men with low testosterone levels should be pretreated with testosterone before being given sildenafil or should be given the 2 therapies together. Another study, by Rosenthal and colleagues,[88] also showed promising results for the use of this combination in men with low testosterone levels who have failed sildenafil. Taken together, these data reinforce recommendations that a serum testosterone measurement be conducted in all men who are being evaluated for ED.

Burnett and Becker,[89] from Johns Hopkins, examined the potential of immunophilins to repair “injury" to the cavernous nerves that may occur during a radical prostatectomy. In an animal (rat) model of ED in which cavernous nerves were either excised or transected, rats that received a non-immunosuppressant immunophilin ligand (GPI-1046) demonstrated “better" erections post-injury. These compounds hold promise as an addition to the perioperative management of patients with prostate cancer who undergo radical prostatectomy.

Padma-Nathan and colleagues[90] also addressed the topic of impotence following radical prostatectomy. Men who had undergone bilateral nerve-sparing radical prostatectomy received sildenafil or placebo, 4 weeks post-surgery, nightly for 36 weeks. Erectile function was then assessed by a variety of outcome measures. Results showed that treatment with this PDE-5 inhibitor significantly increased the percentage of men who had return of spontaneous erections (27% vs 4%). The mechanism of this improvement was not explained, and further research is needed before a carte-blanche recommendation is made for such treatment in all post–radical prostatectomy patients.

Steidle and colleagues[91] reported data on a new testosterone gel (Testim™, Auxilium, Norristown, PA) demonstrating its efficacy in raising serum testosterone levels and improving certain hypogonadal symptoms.

Peyronie’s Disease

Davila and colleagues,[92] from the University of California, Los Angeles, introduced a new animal (rat) model to investigate the role of fibrin in Peyronie’s disease. It has been postulated that fibrin is the initiator of the fibrotic cascade in men with Peyronie’s disease. This pro-fibrotic protein supposedly extravasates from the blood into the tunica albuginea of the penis following an injury and, for some reason, is not degraded and continues to promote fibrosis. This new fibrin animal model may allow for the in-depth investigation of novel therapies for this relatively unknown urologic disorder.

[Jacob Rajfer, MD]

It has been postulated that fibrin is the initiator of the fibrotic cascade in men with Peyronie’s disease.

Emerging Technology: Proteomics and SELDI

The differential expression of proteins within healthy and diseased states represents the field of proteomics. At this year’s meeting of the AUA, a number of abstracts described the application of emerging technologies designed to identify protein differences as they occur between normal and diseased states. A proteomic technology that has the potential to contribute to the discovery of new clinically relevant biomarkers is surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectroscopy.

Using mass spectroscopy–based proteomics, Liu and associates[93] described the identification of differentially expressed proteins unique to prostate cancer cells. Utilizing tissue specimens obtained following radical prostatectomy, the authors compared the protein profiles of cells within paired sections of normal, BPH, and cancer specimens using SELDI-TOF mass spectroscopy. The expression of a protein with an average mass unit of 24 kd was identified in 16 (94%) of the 17 prostate cancer specimens. All of the normal and BPH specimens failed to demonstrate the expression of this protein. Although the nature of this protein has yet to be identified, this study represents the potential of this new technology to aid in the discovery of new biomarkers.

Gretzer and associates[94] presented work utilizing SELDI-TOF mass spectroscopy following preprocessing with molecular separation and chemical fractionation of cell membrane extracts from 3 Dunning rat prostate cancer cell lines of varying metastatic potential to search for novel proteins that are differentially expressed. SELDI analysis of the membrane preparations from each of the cell sublines showed differences when the extracts from the metastatic sublines were compared with those from the benign cell lines. These differences included 4 notable changes in peptide expression, one of which was the identification of a 17 kd peptide that was unique to the metastatic cells.

The investigators also demonstrated the potential of sample preprocessing

prior to SELDI analysis utilizing molecular ultrafiltration and ammonium sulfate precipitation to improve the resolution of the heterogeneous protein samples and aid in subsequent candidate biomarker isolation and identification. Current efforts are underway utilizing these methods to isolate, purify, and characterize the 17 kd overexpressed peptide identified with SELDI-TOF.

SELDI technology may also assist with the identification of protein changes between invasive and noninvasive bladder tumors. Langbein and associates[95] presented work demonstrating the potential for proteome analysis and profiling to detect differences between superficial and invasive bladder carcinomas. SELDI analysis of tissue extracts obtained from 9 Ta and 5 T3 bladder tumors revealed differential expression of a 10 kd protein in the noninvasive bladder tumors and upregulation of 5 proteins among the invasive tumors (7.4 kd, 9.5 kd, 14.5 kd, 15.1 kd, and 15.9 kd). Confirmation of these findings with larger studies will undoubtedly benefit the diagnosis and prognosis of bladder cancers, given the current lack of biomarkers within this area of urologic oncology.

RCC is another urologic malignancy for which there are currently no clinically applicable biomarkers. Rogers and associates[96] employed SELDI proteomic technology to identify urinary biomarkers for RCC. Urine was collected from patients with RCC (n = 60), age-matched healthy controls (n = 49), and patients with benign urologic pathology (n = 29). SELDI analysis identified differences in the profiles among all 3 groups. Although no individual protein was identified as unique to one group, neural network analysis of the spectra from each group provided discrimination of cancer from control with a sensitivity of 97% and a specificity of 99%.

In addition to cellular- and tissue-based expression profiles, serum proteomic patterns continue to demonstrate promising diagnostic potential. Banez and associates[97] utilized SELDI mass spectrometry to evaluate the complex protein profiles of 106 men with prostate cancer and 56 men free of disease. Two SELDI ProteinChip arrays were used to generate a combined spectral database that obtained a sensitivity of 85%, a specificity of 85%, and a positive predictive value of 93% on validation within an internal test set. The investigators employed a computer-based decision-tree algorithm to aid in discrimination of the SELDI-generated protein profiles from the 2 groups of patients. Although these results are preliminary, they support the use of pattern profiling as a mode to discriminate between 2 groups of patients.

SELDI technology may also assist with the identification of protein changes between invasive and noninvasive bladder tumors.

Ornstein and associates[98] also presented a study demonstrating the diagnostic potential of SELDI-generated serum protein profiling. These authors obtained serum from 114 men (PSA 2.5-14.0 ng/mL [n = 108] and PSA <2.5 ng/mL with suspicious digital rectal exam [n = 6]) prior to prostate biopsy. The SELDI-generated profiles from these men were then analyzed using a pattern-recognition algorithm. The serum samples were divided into a test set (randomly selected) to train the diagnostic algorithm and a blinded set for diagnostic evaluation. In the blinded set, all men with cancer on biopsy were correctly identified by SELDI proteomic analysis, whereas 68% of men with benign biopsies were correctly identified. These studies corroborate previously published articles showing that analysis of serum protein profiles by SELDI mass spectroscopy may aid in the discrimination of men with prostate cancer from those without prostate cancer.

Beiko and associates[99] demonstrated the potential for SELDI to aid in screening for urolithiasis. The association of certain proteins with urolithiasis may offer insight into detecting patients with stone disease or at risk for developing stone disease. Urine samples were obtained from 25 men with stone disease and 25 men without any history of urolithiasis. Total urinary protein, oxalate levels, and SELDI-generated protein profiles were determined and compared. Among the men with stone disease, total protein and oxalate levels were found to be significantly higher than in the control subjects. Furthermore, the protein profiles generated by SELDI revealed differential expression of 2 proteins between the groups (24 kd and 67 kd). A ratio of expression was determined for these 2 proteins. Patients with stone disease expressed more of the 67 kd protein and less of the 24 kd protein. The converse was found among the SELDI spectra for urine obtained from patients without a history of stone disease. This study represents yet another novel application of proteomic technology to differentiate among disease states. Further work corroborating these results is anxiously awaited.

SELDI technology overcomes many of the limitations of traditional protein analysis methods by enabling rapid analysis of small amounts of crude protein specimens from a variety of biologic sources. Although

these early results are encouraging, the bioinformatic technology used to interpret the changes in protein expression among specimens from different disease states requires validation from additional sources.
[Matthew B. Gretzer, MD, Alan W. Partin, MD, PhD]

52nd Annual Meeting of the Society for Pediatric Urology

The Society for Pediatric Urology held its 52nd annual meeting on April 26, 2003, just prior to the 2003 meeting of the AUA. Three presentations were especially noteworthy.

Prepubertal Testis Tumor Registry

Jonathan Ross, MD, presented the findings of the American Academy of Pediatrics (AAP) Section on Urology Prepubertal Testis Tumor Registry, which has been ongoing for the past 2 decades.[100] Treatment of prepubertal testis tumors has previously been based on experience with adult testis tumors. However, data from the Prepubertal Testis Tumor Registry demonstrate that prepubertal and adult testis tumors differ in their pathologic and clinical behavior. Yolk sac tumors, which present at around age 16 months, comprise 62% of the 395 prepubertal testis tumors reported to the registry. Alpha-fetoprotein (AFP) is elaborated in 90% of yolk sac tumors preoperatively, and most tumors (80%) are stage I. Only 25% of patients with metastatic disease have disease limited to the retroperitoneum. An AFP that remains elevated postoperatively suggests metastatic disease. It is important to note that AFP is normally elevated to 50,000 ng/dL in newborns and then decreases to several hundred ng/dL. By around age 5 months, AFP level should be only 50 ng/dL. When AFP remains abnormally elevated, chemotherapy can effectively eradicate metastases and obviate the need for routine retroperitoneal lymph node dissection.

Teratomas

H. Gil Rushton, Jr, MD, presented the Children's National Medical Center's experience in testis-sparing enucleation for teratoma and epidermoid cysts.[100] Teratomas constitute the second most common prepubertal testis tumor reported to the AAP registry; however, they are the most common prepubertal testis tumors in multiple single-institutional experiences. Pediatric teratomas do not stain for AFP, nor are AFP levels elevated. Metastatic disease has not been reported in either immature or mature teratomas.

Over the past decade, testis-sparing enucleation has been employed for teratoma and epidermoid cysts. Rushton and colleagues[101] reported no recurrences in a median follow-up of 8 years. Pathologic examination demonstrated negative AFP staining, no multifocal tumor, and negative placental alkaline phosphatase staining (marker for carcinoma in situ) in surrounding testicular tissue.

There are theoretical concerns, however, regarding tumor seeding and spillage, incorrect pathologic diagnosis, frozen sectioning errors, and residual multifocal disease. A retrospective study from the Armed Forces Institute of Pathology Testis Tumor Registry dispels some of these concerns.[101] This review reports on 17 prepubertal teratomas treated with radical orchiectomy and followed for 3 months to 8 years. There were no recurrences in this group. Only 0.8% of all testis tumors in the registry showed mixed histology (yolk sac tumor and teratoma), and the yolk sac histology predominated in both of these cases.

An important take-home message is that unless the patient is older than 1 year and presents with a preoperatively elevated AFP level, the surgical approach to teratomas should start with an excisional biopsy, when possible, as testis-sparing surgery is safe and effective in the majority of cases.

Febrile Urinary Tract Infection and Vesicoureteral Reflux

A recent study from the *New England Journal of Medicine* questioned the need for routine imaging in children with febrile urinary tract infection (UTI).[102] Jack Elder, MD, provided compelling evidence for the need for voiding cystourethrography (VCUG) following febrile UTI in children.[103] He cited the incidence of reflux in children with febrile UTI to be as high as 50%. Dimercaptosuccinic acid (DMSA) scans may be positive in as many as 80% in some series. Kidneys with grade III to V vesicoureteral reflux (VUR) were twice as likely to show acute pyelonephritis as were kidneys with grade 0 to II VUR. VUR increased the risk of acute pyelonephritis depending on calyceal anatomy and epithelial cell receptors for *P fimbriae*. The risk of scarring increased almost exponentially with the number of UTIs.

Kidneys with grade III to V vesicoureteral reflux (VUR) were twice as likely to show acute pyelonephritis as were kidneys with grade 0 to II VUR.

Dr Elder cited a study from Australia and New Zealand that demonstrated a slight increase in end-stage renal disease (ESRD) secondary to reflux nephropathy. This study concluded that treatment of VUR has no significant impact on ESRD.[104] Two recent studies demonstrated that

only 4% of ESRD in children is associated with reflux nephropathy; of 224 patients, only 2 of 9 patients with reflux nephropathy had UTIs and 4 patients had VUR of grade III or lower.[105,106] However, reflux treatment has been shown to impact the incidence of ESRD in Sweden: since 1986, the incidence of ESRD in patients with reflux has been 0%, whereas from 1978-1985, the incidence was 5%.[107]

Long-term follow-up of adult female patients with pyelonephritis shows that there is an ongoing risk of scarring, even with previously normal kidneys, with the greatest risk factors being recurrent clinical pyelonephritis and VUR. In the past, studies of randomized series of children with moderate or severe VUR have shown a risk of 15% for new renal scarring in patients who received antibiotic prophylaxis or surgical ther-

Main Points

- Results of a study of a rat model of depression support the hypothesis that depression is linked to overactive bladder and idiopathic urge incontinence. Adult female rats treated with clomipramine demonstrated increased voiding frequency, decreased bladder capacity, and unstable bladder contractions. Treatment with fluoxetine reversed these effects.
- Results of recent studies support the theory that calcium phosphate deposits within the kidney serve as a nucleating site for calcium oxalate.
- Two prospective, randomized trials of α-blocker therapy (ie, alfuzosin, terazosin) in patients with chronic prostatitis/chronic pelvic pain syndrome demonstrated statistically significant improvement in domains of the NIH Chronic Prostatitis Symptom Index compared with placebo. Results indicate that long-term α-blocker therapy is required to achieve a treatment effect and to prevent relapse.
- Several abstracts pointed out deficiencies in the American Joint Commission on Cancer TNM (tumor-node-metastasis) pathologic staging system and suggested alternative groupings. For example, studies show that patients with renal tumors that have invaded the adrenal gland (classified as stage T3a) have a significantly worse rate of survival than those with tumors that have invaded the renal fat (also classified as stage T3a); it has been suggested that stage T3a tumors with adrenal involvement be reclassified, perhaps as stage T4.
- A large number of men with significant prostate carcinoma have total prostate-specific antigen (PSA) levels below the standard cutoff point for biopsy of 4.0 ng/mL. However, when the cutoff point is lowered, lack of specificity becomes problematic. Studies have suggested that the use of complexed PSA measurement may increase specificity in patients with lower PSA levels (2.0-4.0 ng/mL).
- The uPM3 test, a new molecular assay for prostate cancer utilizing urine samples, detects expression of PSA mRNA, as a marker of prostate cells, and PCA3 mRNA, which is selectively expressed in the majority of prostate cancer patients. In 2 studies, the uPM3 test was shown to enhance specificity over PSA measurement.
- A newly developed, easy-to-use nomogram, the Vienna nomogram, has been shown to effectively define the optimal number of biopsy cores based on age and prostate volume and significantly improve prostate cancer detection.
- Serum PSA level is a useful clinical predictor of the natural history of benign prostatic hyperplasia in terms of future prostate growth, symptomatic worsening, progression to urinary retention, and progression to invasive surgery.
- Large-scale, cross-sectional, longitudinal epidemiologic observations strongly suggest that lower urinary tract symptoms (LUTS) in aging men correlate with various domains of sexual dysfunction. Patients presenting with either sexual dysfunction or LUTS should be screened for the presence of associated symptomatology.
- Studies have shown that varicocele repair and vasectomy reversal are both viable solutions to the problem of male factor infertility; even in couples in which the interval of vasectomy obstruction is longer than 15 years and the female partner is as old as 40 years, these procedures offer a viable alternative to in vitro technology.
- Studies on the treatment of erectile dysfunction (ED) have shown improved outcomes for men with low testosterone levels who received both testosterone and sildenafil, compared with those who received sildenafil alone. Serum testosterone measurement should be considered for all men who are being evaluated for ED.
- Preliminary results of studies utilizing surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectroscopy support the potential of this technology to aid in diagnosis of diseases, such as prostate cancer and urolithiasis, as well as differentiation of various disease states, such as invasive versus noninvasive bladder tumors.
- Unless the patient is older than 1 year and presents with a preoperatively elevated alpha-fetoprotein level, the surgical approach to teratomas should start with an excisional biopsy, when possible, as testis-sparing surgery is safe and effective in the majority of cases.

apy.[108] A significantly reduced risk of pyelonephritis has been demonstrated in patients who undergo surgical therapy and do not receive antibiotic prophylaxis. Results of more recent studies indicate that the risk of renal scarring, as determined by DMSA scanning, is only 1% to 2% following successful surgical therapy.[109,110] Therefore, appropriate antibiotic therapy, attention to bowel and bladder function, and surgical intervention, when indicated, have improved outcomes for patients with UTI and VUR. VCUG remains instrumental in determining which patients are at highest risk for long-term renal damage following a febrile UTI and helping to define the extent of long-term prophylaxis. ■

[Ellen Shapiro, MD, FACS, FAAP]

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